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PLENARY LECTURE

Cognition in the Era of Technology: "Seeing the Shades of Gray"

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The enormous impact of the so-called technology explosion in cardiovascular medicine is well known. Figure 1 reminds us that the cognitive aspects of our specialty have expanded in concert with technology and that patients who we used to see only in terms of black or white are now routinely evaluated in terms of the broad spectrum between the extremes. Our task as cardiovascular specialists is to locate the appropriate diagnostic and therapeutic shade of gray for each patient. My theme today is that cognitive issues are more dominant in this process than we often realize. I hope to illustrate this point by discussing two of our most commonly used technologies, coronary arteriography and studies of myocardial perfusion, as they relate to coronary artery disease.

Figure 2 reminds us that patient care decisions in coronary artery disease usually involve considerations of arteriographic status, left ventricular function and the individual clinical profile. The clinical profile, of course, includes a number of pertinent variables, and perfusion studies are only one of these. Let us begin, however, by considering coronary arteriography.

Coronary Arteriography

Relations among coronary stenosis, resistance and flow. Figures 3 and 4 make two general points about the functional implications of individual arteriographic lesions. The first relates to the relation between stenosis resistance and flow. As technically superior arteriography has become routine, engineers and cardiologists have developed information that allows us to think about coronary stenoses much as we have traditionally thought about valvular aortic stenosis. As with aortic stenosis, the pressure gradient across a coronary stenosis increases with flow in a nonlinear fashion, a phenomenon called flow separation. When the pressure gradient across the stenosis is plotted against flow, the relation is therefore curvilinear. Imagine that the relation shown in Figure 3 represents a 70% diameter stenosis associated with effort-induced angina. Stenosis resistance can be expressed as the tangent to the relation at any given level of flow. As flow increases with effort, stenosis resistance also increases, as reflected by the steeper slope of the tangent at the point of increased demand versus the basal tangent. Thus, the functional severity of even a rigid stenosis increases with effort, and the symptomatic implications of any stenotic lesion depend in part on the degree of activity a patient is likely to achieve.

Functional importance of small differences in degree of stenosis. In Figure 4 (left), the pressure gradient across the stenosis is again plotted against coronary flow, with relations shown for 30%, 50%, 80% and 90% as well as 70% diameter stenoses. The tangents to these relations reflect stenosis resistances at a given level of flow. In Figure 4 (right), individual values of stenosis resistance are plotted against degree of stenosis. Resistance increases relatively slowly below 70% diameter narrowing, but then almost doubles between 70% and 80% and doubles again between 80% and 90%. Even with technically excellent arteriograms, I think that few of us would want to bet the house, so to speak, on our ability to distinguish between stenoses in this range. It is not surprising, therefore, that patients with apparently similar lesions on arteriography can vary greatly in their clinical presentation. The issues raised by Figure 4 concern more than differences in arteriographic interpretation, however, and we need to consider next factors that can change the caliber of a stenosis from moment to moment.

Dynamic changes in degree of stenosis. We all recognize that many atherosclerotic coronary lesions are eccentric, with portions of the vessel wall that remain susceptible to constrictor or dilator effects of vascular smooth muscle. One important example of vasodilation was provided by the careful studies of Brown et al. (1) in the early 1980s. With use of quantitative arteriographic measurements of the cross-sectional area of the lumen of human coronary stenoses, these investigators demonstrated that luminal area increases systematically in response to intracoronary or sub-

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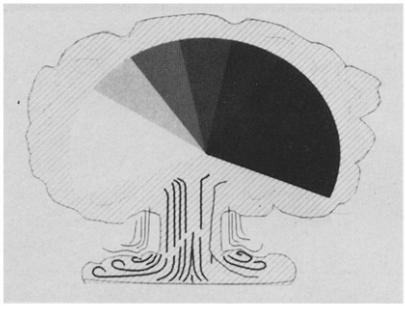


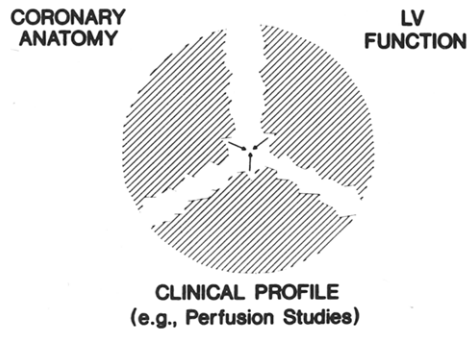
Figure 1. The "technology explosion" exposes the diagnostic shades of gray.

lingual nitroglycerin and that stenosis vasodilation plays an important role in the clinically beneficial effects of nitroglycerin.

On the other side of the coin, a substantial body of evidence now indicates that dynamic reductions in the caliber of a stenotic lumen often play a crucial role in acute ischemic syndromes. The list of possible vasoconstrictor agents includes serotonin, thromboxane A_2, histamine, endothelin and platelet-related factors, among others. A small thrombus can also narrow a stenotic lumen crucially and play an important role in at least some acute ischemic syndromes. As a thrombus is being formed, platelet activation serves as an amplifying factor for the release of vasoconstrictor substances and a vicious cycle of increasing luminal compromise is easily visualized. Paradoxic vasoconstrictor responses are also possible. Normal endothelium produces a dilator substance, endothelium-derived relaxing factor, which is importantly involved in normal flow regulation and which mediates the vasodilation normally occurring when acetylcholine is injected into a coronary artery. When endothelium is damaged, however, the normal dilator response to acetylcholine can be reversed.

A study of Ludmer et al. (2) illustrates this latter point. When acetylcholine was injected into a normal coronary artery, the epicardial portion of the artery dilated to a modest but statistically significant degree. The artery also

Figure 2. Factors influencing patient care decisions in coronary disease. LV = left ventricular.



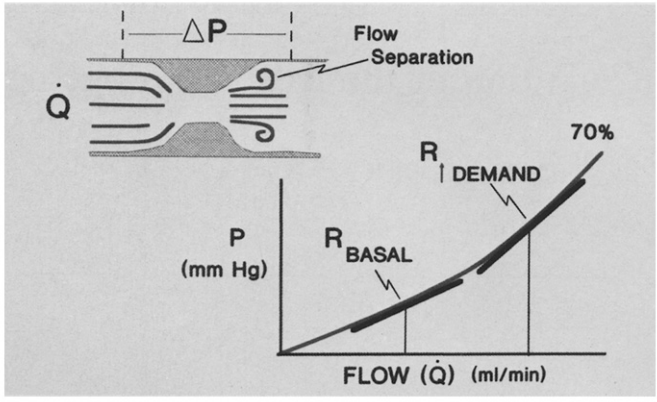
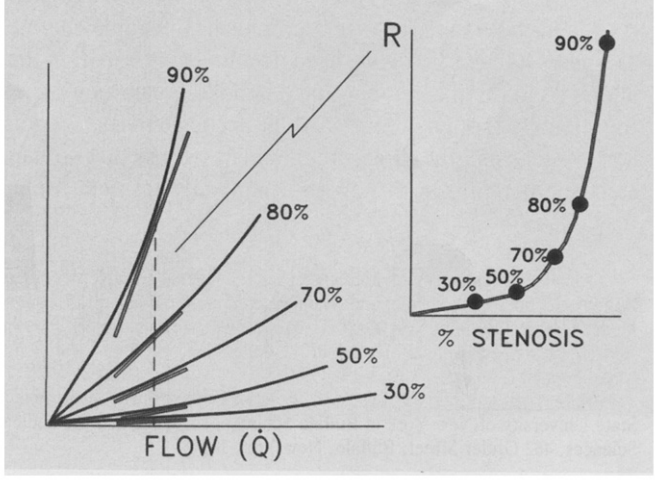


Figure 3. Flow-related changes in functional severity of a coronary stenosis (see text). ↑ DEMAND = increased demand; ΔP = pressure gradient across the stenosis; Q̇ = coronary flow; R = stenosis resistance.

showed the usual dilator response to intracoronary nitroglycerin. In patients with coronary disease, acetylcholine constricted rather than dilated the coronary artery, producing as much as a 75% reduction in diameter in the stenotic segment itself and a 50% reduction in diameter immediately proximal to the stenotic segment. This paradoxic constrictor response to acetylcholine occurred in the presence of a retained normal dilator response to nitroglycerin.

Interpretation of coronary arteriographic images: role of quantitative arteriography. While considering cognitive issues relating to the interpretation of arteriographic images, we should also discuss the conventions used to describe individual lesions. Percent diameter stenosis, the traditional and still most commonly used standard, is of course measured as the maximal percent luminal narrowing in any single arteriographic view and is obtained by comparing luminal

Figure 4. Functional importance of small differences in degree of stenosis (see text). Abbreviations as in Figure 3.



diameter at the point of maximal narrowing to luminal diameter in an adjacent portion of the same artery.

I also referred earlier to quantitative arteriography. In this approach, cross-sectional area at the point of maximal narrowing is calculated in absolute values, that is, in square millimeters, with use of orthogonal views and the assumption of an elliptic luminal shape. The advantage of expressing luminal area in absolute rather than relative terms is that the arteriographer avoids using the lumen adjacent to the stenosis (which is itself involved in the atherosclerotic process) as a reference in the calculation of percent stenosis. For example, an absolute luminal area that might represent an 80% narrowing in an otherwise normal artery could appear as only a 40% stenosis in an artery with a diffusely thickened wall if the overall vessel diameter were unchanged.

Quantitative arteriography has unquestioned value in sequential assessments of an individual lesion, for example, before and after nitroglycerin administration. Quantitative arteriography does have an important limitation for routine diagnostic use, however, in that it is difficult to judge whether any specific absolute value of luminal area is normal or abnormal. Arterial dimensions, including luminal cross-sectional area, normally decrease progressively as one proceeds proximally to distally, from base to apex of the ventricle. Dimensions also vary from patient to patient depending on the pattern of coronary artery branching, gender, body size and presence or absence of ventricular hypertrophy. Because of the difficulty in determining whether an absolute value of luminal area is normal or abnormal, some arteriographers have switched to reporting relative rather than absolute narrowing and speak of percent reductions in cross-sectional area. This probably does not offer any important advantage over the traditional measurement of percent diameter stenosis.

Remodeling of the sclerotic arterial wall. A final consideration in attempts to quantify arteriographic lesions is that atherosclerosis involves a complex remodeling of the entire arterial wall. Many of us have thought about coronary lesions solely in terms of atherosclerotic proliferation, implicitly expecting a one to one correlation between amount of atherosclerotic material and reduction in luminal size. It is now clear, however, that the atherosclerotic process proceeds in an outward as well as inward direction, and involves an increase in external arterial diameter as well as a reduction in luminal diameter.

Figure 5 further illustrates the remodeling process. This figure has been prepared with use of data from a recent study by Stiel et al. (3) in Hamburg of human coronary arteries fixed at a normal arterial pressure. The proximal portion of a normal artery is shown on the left and a stenotic atherosclerotic artery on the right. The internal elastic membrane lies at the base of the intima. If we compare the two arteries at point A, we see that the atherosclerotic process does encroach on luminal area, but that the degree of encroachment

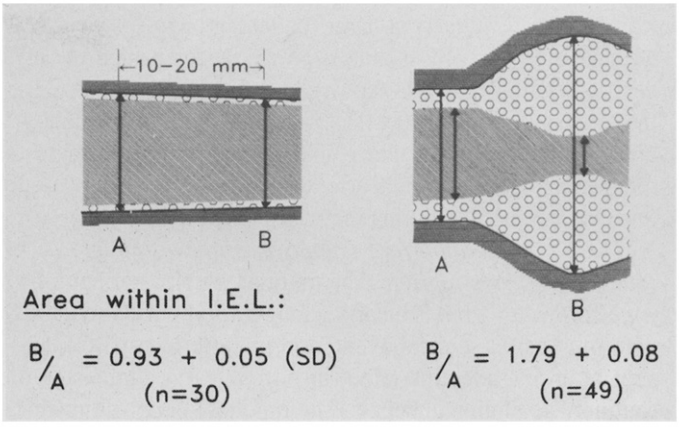


Figure 5. Schematic representation of atherosclerotic coronary artery remodeling. **Left**, Normal coronary artery. **Right**, Sclerotic coronary artery. I.E.L. = internal elastic lamina (**thin solid line**). (Adapted from data of Stiel et al. [3].)

is attenuated by an increase in overall arterial diameter. When we look at point B in the diseased artery, we see that atherosclerotic enlargement is accentuated at points of clinically recognizable stenosis. This local increase in degree of enlargement can be expressed in terms of the ratio of the areas contained within the internal elastic membrane at points B and A. In the Hamburg series of patients (3), this ratio averaged 1.79 in diseased arteries, as opposed to 0.93 in nondiseased normally tapering arteries. Because the remodeling process is just beginning to be considered by cardiologists as well as pathologists, its implications for routine arteriographic measurements are not yet clear. Note, however, that the percent luminal narrowing that would be calculated on routine arteriography depends on the relative luminal diameters at points A and B in the atherosclerotic artery. Each diameter is the end result of a process involving both atherosclerotic proliferation and overall arterial enlargement. The degrees of proliferation and enlargement at the two points differ substantially, however. Factors underlying these local differences in degree of proliferation and enlargement have an important effect on arteriographic measurements of percent stenosis and need to be understood more fully. The issues raised by Figure 5 may also affect arteriographic studies of lesion progression or regression, or both.

Clinical implications: cognitive issues in interpretation. Coronary arteriography routinely provides technically excellent views of arterial luminal configuration. The presence or absence of disease, the location and extent of disease and the amount of myocardium at risk are reliably defined. The exclusion of disease often has long-term cost-effectiveness as well as clinical value. Arteriography defines the anatomic possibilities for revascularization when clinically appropriate. When sequential arteriographic studies are available, progression or regression, or both, of luminal abnormalities can also be examined. Prognostic information can be derived

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from reported studies of large patient groups, particularly because arteriography is almost always accompanied by left ventriculography and left ventricular function is recognized as the single most powerful predictor of survival in risk stratification. Finally, the test of time is in many ways the ultimate test for any new technology and arteriography has certainly passed this test successfully during the past 2 decades.

There remain important cognitive issues in the interpretation of any arteriogram. The point at which arteriography is performed in what is clearly a long-term disease is usually determined by a clinical event, and the arteriographic snapshot often includes the effect of nitroglycerin administered routinely as filming is begun. The functional implications of a stenosis always require careful clinical correlation. Functional severity varies with both coronary flow and small changes in degree of stenosis. Dynamic changes in degree of stenosis are frequent and involve both thrombus formation and effects of a variety of vasoactive substances. All approaches for quantifying the degree of stenosis have substantial limitations and some of us feel that these are unlikely to be surmounted by new radiographic approaches. Complex issues also arise in extrapolating information derived from studies in patients with stable angina to those with acute ischemic syndromes. Patients with acute syndromes form a substantially larger proportion of individuals undergoing arteriography now than they did only a few years ago, and many arteriographers believe that the surface configurations of lesions differ systematically in acute and chronic situations. Although we often have no better option than to extrapolate from findings in patients with stable angina studied in the late 1970s and early 1980s, there are special challenges in doing so. Arteriography seems particularly limited with respect to management decisions that involve a judgment about the short-term likelihood of a new thrombus.

Studies of Myocardial Perfusion

In view of the material just presented, there remain—even in 1990—many shades of gray to be distinguished in the use of arteriographic information in individual patient care decisions. Studies of myocardial perfusion are intended to assist in such decisions by defining the functional end result of whatever arteriographic abnormalities are present. The variety of approaches to perfusion imaging included in the scientific program at this College meeting attests to the importance and still evolving nature of perfusion technology. Although time does not permit a detailed discussion of strengths and limitations of individual techniques, I would like to address interpretive issues that are common to most techniques by considering them in the context of coronary flow reserve.

The coronary flow reserve concept. In Figure 6 coronary flow is plotted against coronary artery pressure. In the normal situation under conditions at rest (large circle), with flow designated as 1.0 (left), the epicardial coronary arteries

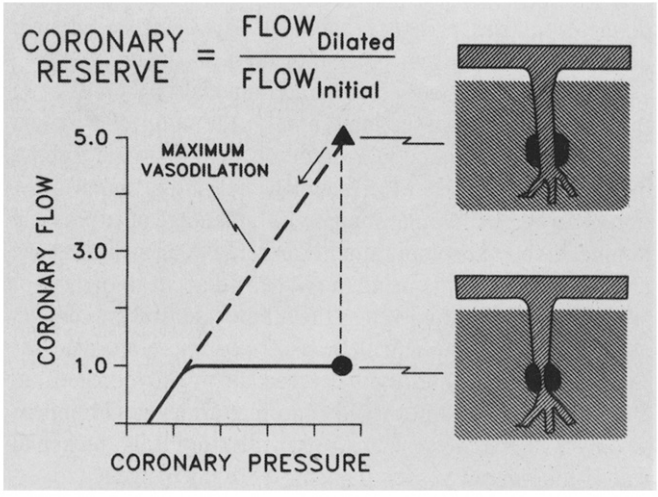


Figure 6. The concept of flow reserve (see text).

are widely patent and, as shown by the stylized vascular smooth muscle (right), there is a high degree of vascular tone at the arteriolar level in the microcirculation. If this tone is abolished, for example, by dilating the peripheral coronary bed with papaverine or dipyridamole, coronary flow can increase fivefold (large triangle and maximally dilated arteriole). Coronary flow reserve is defined as the ratio of flow during maximal vasodilation to flow under initial conditions at rest. The dashed line (Fig. 6) represents the relation between flow and pressure during maximal vasodilation over a wide range of pressures. The absolute value of flow reserve will vary if vasodilation is accompanied by a change in arterial pressure. For example, if dipyridamole were used as the dilating agent, a small decrease in arterial pressure would not be surprising and the value of flow reserve measured might be closer to 4 than to 5.

Coronary flow reserve in coronary stenosis. Figure 7 indicates how coronary vasodilator reserve compensates for effects of epicardial coronary stenoses under conditions at rest. Coronary flow is again plotted against coronary artery pressure. As in Figure 6, flow at rest is designated as 1.0 and the normal coronary pressure-flow point is shown by a large circle. The horizontal distances between the normal operating point and the various degrees of stenosis (smaller circles) reflect the pressure gradients across the stenoses under conditions at rest. As shown by the diagrams above the graph, progressive arteriolar vasodilation allows flow to be maintained until stenosis diameter is narrowed by more than 90%. Because a portion of arteriolar vasodilator reserve is used to maintain flow at the normal level, less reserve remains when vasodilation is induced.

Figure 8 illustrates more clearly why measurements of flow reserve seem so attractive for defining the functional significance of a stenosis independent of arteriography. Flows at rest and after vasodilation for individual lesions are connected by the thin dashed lines, which are curvilinear

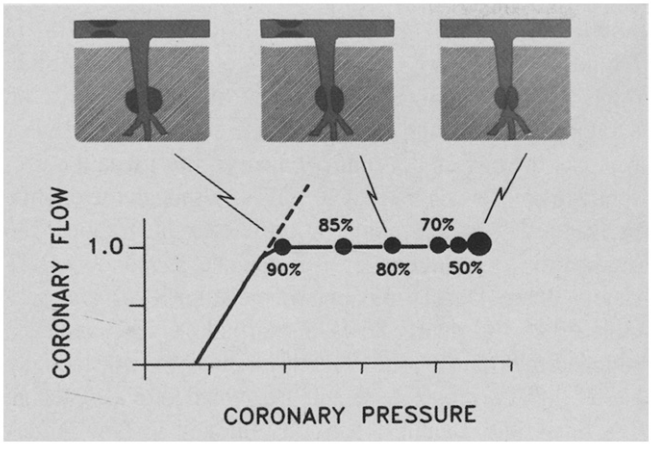


Figure 7. Use of coronary vasodilator reserve to compensate for effects of coronary stenoses under basal conditions. Progressive arteriolar vasodilation (**top diagrams**) allows coronary flow to be maintained until stenosis diameter is narrowed to >90% (**circles on graph**) (see text).

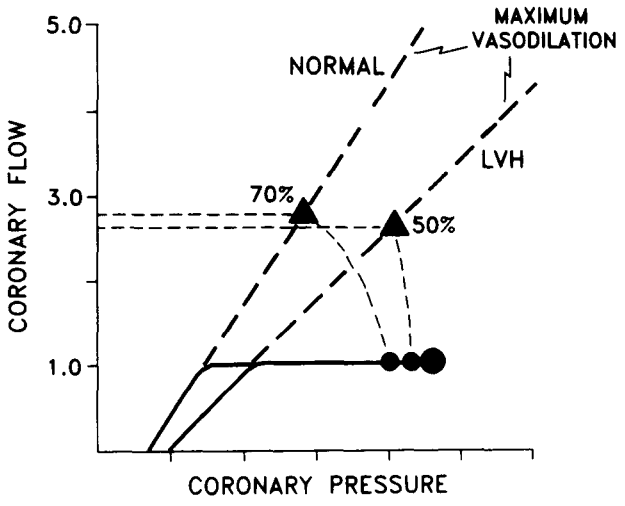
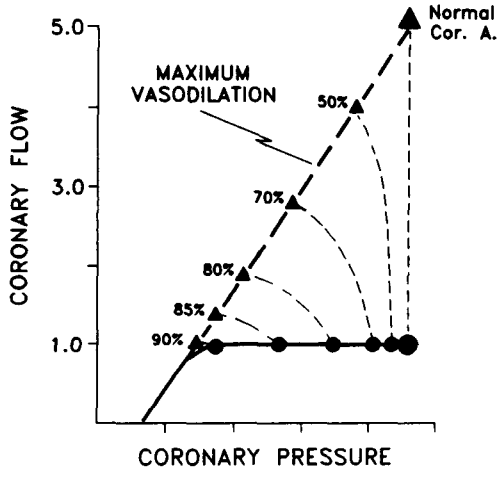


Figure 9. Hypertrophy-induced shift in the pressure-flow relation during maximal vasodilation. Directionally similar shifts can also be caused by myocardial scarring, tachycardia, increased ventricular preload and other factors (see text). LVH = left ventricular hypertrophy.

because of the effects of flow separation mentioned earlier. The amount of flow that can be achieved during maximal vasodilation varies inversely with the degree of stenosis. On first glance, it would appear that stenoses in the clinically difficult range between 50% and 90% should be readily separated by a numeric measurement of flow reserve. With use of the Doppler technology developed by the late Melvin Marcus (4), who is missed at this meeting by all of us, it is now possible to obtain numeric measurements of flow reserve in individual coronary arteries. In any one patient, however, the numeric value of flow reserve varies not only with changes in arterial pressure, as noted earlier, but also with changes in other hemodynamic variables such as heart rate and ventricular preload. Additional confounding factors in coronary disease are myocardial scarring and ventricular hypertrophy. Growth of vascular channels does not always keep pace with hypertrophy of muscular elements, leading to the situation shown in Figure 9.

Figure 8. Use of coronary flow reserve to evaluate the functional significance of stenotic lesions. Coronary flows at rest and after vasodilation for individual stenotic lesions are connected by **curvilinear dashed lines** (see text). Cor. A. = coronary artery.



Role of ventricular hypertrophy. Figure 9 points out that the position of the pressure-flow relation during maximal vasodilation changes substantially with ventricular hypertrophy. The magnitude of the shift shown is that expected for a 30% increase in left ventricular mass, as derived from measurements in hypertensive patients by Strauer (5). The numeric value of flow reserve in Figure 9 is essentially identical for a 70% stenosis in a normal ventricle and a 50% stenosis in the hypertrophied ventricle. A number of pathologic studies (6) suggest that hypertrophy of this degree is the rule rather than the exception in coronary disease and has already developed in individuals whose initial manifestation of coronary disease is sudden death.

Clinical implications of flow reserve measurements. Before concluding our discussion of numeric values of flow reserve, we should note an important difference in the use of these measurements by the practicing cardiologist as compared with the clinical investigator. The Iowa group (7) has collected Doppler velocity probe data that nicely define the reciprocal pathophysiologic relation between flow reserve and degree of stenosis in humans. In establishing this relation, the investigators chose, quite understandably, to include only patients with a discrete single stenosis rather than arteriographically diffuse disease and to exclude patients with myocardial hypertrophy, left ventricular dysfunction, previous myocardial infarction or angiographically apparent collateral circulation, as each of these factors might have

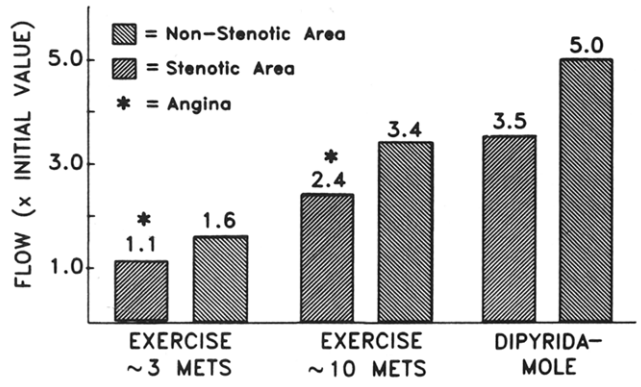


Figure 10. Examples of 30% reductions in regional myocardial flow, which have different clinical implications. **Left**, Exercise with angina at a low work load. **Center**, Exercise with angina at a high work load. **Right**, Vasodilation with dipyridamole.

influenced flow reserve independent of the stenotic lesion. A clinician dealing with an individual patient must keep in mind not only these exclusions but also the 95% confidence limits for any individual value of flow reserve. These limits were quite wide in the Iowa study, varying for example from 1.2 to 4.2 in cases of 70% diameter stenosis and from ~3.8 to ~8.2 in individuals without coronary disease.

Interpretation of myocardial perfusion images. Let us next consider coronary flow reserve in relation to perfusion images. Because a clinician is usually trying to identify a regional abnormality in perfusion, techniques that allow comparison of different regions of a ventricle can avoid some of the pitfalls of numeric measurements of flow reserve. When we combine perfusion imaging with a stress test or dipyridamole infusion, we are really trying to determine whether flow reserve is reduced on a regional basis, and we focus on the presence or absence of a regional difference rather than on absolute values. The minimal size of an image defect that can be appreciated is limited by the resolution of each technique and also varies with the physical characteristics of the individual patient. Although there are few data directly addressing the minimal difference in regional flow needed for a defect to be appreciated, a difference of at least 30% is probably needed for most techniques under conditions at rest. In addition, because the myocardial extraction of some commonly used tracers varies inversely with flow, the relative flow difference needed to identify a defect during vasodilation is often greater than at rest.

Figure 10 raises additional interpretive issues by illustrating three situations that might be expected to produce similar defects on perfusion images but that would have significantly different clinical implications, namely, exercise with angina at a low work load, exercise with angina at a high work load and pharmacologic vasodilation. In each case, flow in a portion of the ventricle supplied by a stenosed coronary artery is 30% less than flow in the remainder of the ventricle. Extrapolating from the studies of Kitamura et al. (8) in Minnesota in the early 1970s, the flow of 1.6 times control in the nonstenotic area (Fig. 10, left) would correspond to an exercise level of 3 metabolic exercise equivalents (METs), whereas the flow of 3.4 times control (center) would correspond to an exercise level of 10 METs. Although the relative perfusion deficits are similar in these two illustrations, the therapeutic implications of ischemia at 3 and 10 METs clearly differ. During maximal vasodilation after dipyridamole (Fig. 10, right), flows in portions of the ventricle supplied by nonstenotic vessels should be substantially higher than during exercise and are shown here as reaching five times initial values. A 30% reduction in flow in this situation corresponds to an absolute level of flow that is 3.5 times the initial value and is not accompanied by an increase in myocardial oxygen demand. Here, then, is a perfusion deficit not associated with ischemia. Although it may be diagnostically useful in identifying the presence of an asymptomatic stenotic lesion, it would ordinarily have little therapeutic impact.

One additional comment about perfusion imaging during pharmacologic vasodilation. Figure 10 suggests that this approach might be more sensitive than exercise imaging for identifying stenoses of modest severity, that is, for diagnostic screening. For this actually to be the case, however, the imaging technique would have to be able to distinguish between two high levels of flow, in this case, 3.5 and 5 times values at rest. Data illustrating that such distinctions are not always possible are provided in a recent study of technetium isonitrile by Glover and Okada (9). When myocardial uptake of technetium was plotted against coronary flow in dogs given dipyridamole, myocardial technetium concentration reached a plateau at a flow of 2.0 ml/min per g, that is, about 2.5 times flow at rest, and did not change with further increases in flow. A defect such as that shown in Figure 10 (right) would apparently not be visualized with technetium isonitrile as a tracer for dipyridamole imaging.

One final point about perfusion imaging during vasodilation. Although time has not permitted discussion of transmural variations in perfusion, we all recognize that flow limitations usually begin in the subendocardium, and are more marked in the subendocardium when flow is reduced across the entire myocardial wall. Data to be presented later in this meeting by Canty et al. (10) from our group illustrate the point. When coronary flow was reduced in sequential steps in chronically instrumented dogs during pharmacologic vasodilation, the degree of flow reduction was always greater in the subendocardium than in the full thickness myocardium. Thus, as perfusion scan technology continues to evolve, techniques that have sufficient resolution to assess subendocardial flow selectively may be especially advantageous.

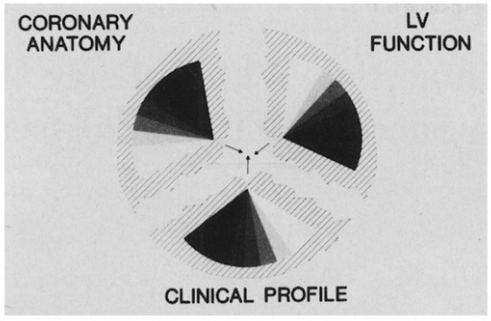


Figure 11. "Shades of gray" in each of the major factors influencing patient care decisions in coronary disease. LV = left ventricular.

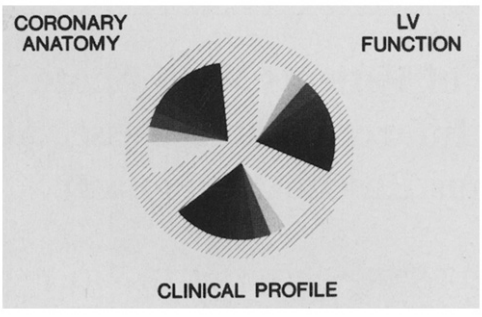


Figure 12. Cognitive synthesis of "shades of gray" in individual patient care decisions. Abbreviation as in Figure 11.

Conclusions: Shades of Gray

In view of the points just discussed, it is fair to say that there are important shades of gray to be discerned in the clinical use of perfusion studies as well as arteriography (Fig. 11). As specific technologies and tracers continue to evolve, it may be helpful to recall what has been termed the "lesson of ejection fraction." When it first became practical to measure ejection fraction clinically, a number of hemodynamic, technical and other potentially confounding factors were identified rather quickly. As we all realize, however, the test of time proved these problems to be either satisfactorily surmounted or clinically unimportant. As we now continue to sort out the relative strengths and weaknesses of newer perfusion technologies, the test of time will no doubt again play an important role in defining the ultimate status of each technology in routine clinical care.

Although I have discussed only one aspect of the clinical profile, several other, at least equally important components must be mentioned. The presence or absence of angina or electrocardiographic abnormalities at rest, or both, and findings on routine stress testing clearly allow patients with coronary disease to be placed in highly relevant clinical subsets. Decisions concerning revascularization often depend on the results of a trial of medical therapy. Risk factor profiles and probabilities of risk factor modification can also influence individual judgments. In some circumstances silent ischemia may be an additional modifying factor. And even when all these issues have been factored into an individual case, another set of considerations arises if the clinician notes a carotid bruit or an enlarged pulsatile aorta, or if patient preferences do not readily coincide with what we consider to be "best medical judgment." Indeed, many would persuasively argue that the spectrum of shades of gray in the clinical profile is even broader than in arteriography or assessments of left ventricular function.

In the last analysis, then, cognition remains the core of cardiovascular medicine even in this era of the technology explosion (Fig. 12). We are still physicians rather than proceduralists and healers rather than fixers. The truly challenging task as we enter the 1990s is to discern among the almost infinite number of shades of gray that we can now identify clinically and technologically and to reconcile them into a cohesive whole for each of the patients we serve. Our opportunity to do so is unparalleled and our responsibility to do so seems equally clear.

I am indebted to C. Richard Conti, MD, our 1989–90 ACC President, for his invitation to deliver this year's Opening Plenary Session Lecture. I also express my appreciation to the many past and present colleagues who have shaped my thinking about the matters discussed.

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